REMARKS

The Office Action dated March 20, 2009 has been carefully reviewed, and the foregoing amendments are made in response thereto. In view of the above amendments and the following remarks, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims.

Status of the Claims

Claim 53 has been amended to recite that the first and second polymerizable mixtures comprises first and second polymerizable materials, respectively, which in turn are partially gelled to form first and second layers of hydrogel, respectively. Claim 53 has also been amended to recite additional crosslinking of the first and second polymerizable materials until the first and second hydrogels further polymerize to form an integrated multi-layered hydrogel. Furthermore, claim 53 has been amended to positively recite that the first and second layers of hydrogel each independently comprise a hydrophilic and synthetic polymer network with high water content. Claim 66 has been amended in a manner similar to the amendments to claim 53. Claims 54 to 56, 62, 65, 67 to 70, and 76 have been amended to be consistent with amended claims 53 and 66 or to perfect formalities.

Support for the above amendments can be found throughout the original disclosure, and specific support can be found at least in the originally filed application as provided in the following table:

Claim Element	Exemplary Support
…polymerizable material…	Page 6, paragraph [0015]; Page 16, paragraphs [0068] and [0069]; and Page 26, paragraph [00108]
…hydrogel…	Title; Page 2, line 3 (paragraph [0004]); Page 6, paragraph [0016]; and Page 13, paragraphs [0048] to [0051].
…partially gelled…	Page 20, lines 3 to 9 (paragraph [0091]); Pages 36 to 37, paragraphs [00131] to [00134]; and

Claim Element	Exemplary Support
	Page 38, paragraph [00138].
…a hydrophilic and synthetic polymer network with a high water content…	Page 2, paragraph [0006]; Page 21, paragraph [0097]; Page 24, paragraph [00105]; and Page 27, paragraph [00110].

Thus, no prohibitive new matter is added to the original disclosure. Upon entry of the amendments, claims 53 to 63 and 65 to 77 remain to be pending.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 53 to 63 and 65 to 77 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al. (US 6,949,252) in view of Sah et al. (US 2003/0077821), Anseth et al. (Journal of Controlled Release 2002), Cooke et al. (US 5,916,585), and Spiro et al.(US 6,773,723). Specifically, the Examiner alleges that one skilled in the art would be motivated to combine the teachings of Mizuno et al. with Sah et al., Anseth et al., Cooke et al., and Spiro et al. to arrive at the present invention.

Applicants have amended claim 53 to recite the formation of an integrated multi-layered hydrogel by partial polymerization of the first and second polymerizable materials, respectively, followed by further polymerization for integration. Amended claim 53 also recites that each layer of the hydrogel independently consist essentially of a hydrophilic and synthetic polymer network with a high water content.

Applicants respectfully submit that the claimed invention, as amended, is not rendered obvious by the combined disclosures of the cited references.

With respect to the primary reference Mizuno et al., the method disclosed therein is markedly different from the claimed method in many aspects including the structural composition and the procedure to prepare a layer containing living cells.

First, Mizuno et al. disclose a multi-layered tissue construct comprising a cellular support matrix which is a sponge-like composition containing many pores, while the multi-layered tissue construct of the present invention is composed of hydrogels which are not sponge-like. Specifically, Mizuno et al. teaches that:

> "As used herein, the term "matrix" refers to a composition comprising a plurality of pores dividing free space into partially enclosed interstices wherein said interstices are in fluidic communication." (column 6, lines 28 to 31)

Mizuno et al. also repeatedly refer to the matrix as "sponge matrix" (column 2, line 66; column 3, lines 12 to 13; column 3, line 47; column 3, line 59; column 6, lines 32 to 33; column 8, line 67; column 11, line 2; and column 11, lines 49 to 51). Furthermore, Figures 2A, 2B, 3A, and 3B show the "honeycomb sponge element of the cellular support matrix" (column 5, lines 5 to 37). In contrast, the claimed invention describes the hydrogels as consisting essentially of hydrophilic and synthetic polymer networks with high water content. Thus, one skilled in the art would readily understand that such hydrogels inherently do not form sponge-like structures.

Regarding the matrix seeded with living cells, Mizuno et al. disclose that it is prepared by introducing the matrix into a solution of living cells such that the solution enters the sponge-like matrix by capillary action (column 2, line 65 to column 3, line 3; and column 3, lines 42 to 51). Mizuno et al. also state that "the cellular support matrix of the present invention acts like a sponge that wicks up (and evenly distributes throughout the intertices of the matrix) cells suspended in a sol-gel solution…" (column 11, lines 49 to 52) Such preparation procedures indicate that the matrix was prepared first and the living cells were added to it afterwards. That is, a cellular support matrix is not crosslinked *in vivo*. In contrast, the claimed method mixes the cells with polymerizable materials to form a polymerizable mixture, i.e., providing a polymerizable mixture, and subsequently the polymerizable mixture is crosslinked to form a partially gelled layer of hydrogel. In other words, the hydrogel layer is crosslinked *in vivo*, as claimed in the present invention.

Mizuno et al. not only differ substantially from the claimed invention, but also fail to provide any disclosure or suggestion which would motivate one skilled in the art to modify the referenced method in such a way so as to arrive at the claimed invention.

The Examiner has noted that Mizuno et al. repeatedly state that the reference method is not limited to specifically disclosed embodiments and that the multilayered design may be fabricated into a variety of forms. It is true that Mizuno et al. made such broad, unsubstantiated, and non-specific statements, but these statements cannot reasonably be interpreted to be that the Mizuno method can be modified in any and all possible ways. Otherwise, Mizuno et al. would render any and all other methods for making multilayer tissue constructs obvious. Particularly, Applicants note that Mizuno et al. state that the referenced method covers "all modifications that are within the spirit and scope of the invention…". (column 25, lines 26 to 30; underline added). Therefore, when compared with the present invention, the Mizuno method, particularly the so-called modification thereof, needs to be considered in light of the Examples and embodiments specifically described in the specification of Mizuno et al., but not to be extrapolated to a unjustifiable proportion. In this regard, the MPEP states that ascertaining the differences between the claimed invention and the prior art requires considering both the invention and the prior art as a whole. MPEP § 2141 II(B).

Turning to the teaching of matrix by Mizuno et al., the definition for the term "matrix" as cited above clearly depicts a matrix having a sponge-like structure. Importantly, this definition is for the Mizuno invention, not merely for one embodiment of Mizuno et al. Mizuno et al. also repeatedly describes sponge-like matrix in the embodiments, preferred embodiments, Figures, and Examples, and are completely silent as to a hdyrogel as claimed in the present invention. Furthermore, the disclosed procedures to seed the matrix with living cells are all based on a sponge-like matrix absorbing a solution of living cells by capillary action. Thus, Mizuno et al. as a whole do not provide any disclosure or suggestion which would motivate one skilled in the art to replace the sponge-like matrix and crosslink the polymerizable material after it is mixed with living cells.

Furthermore, the secondary references fail to cure the deficiencies of Mizuno et al in view of the amended claims.

Spiro et al. disclose bilayer matrices for tissue regeneration wherein the layers are attached to each other by either mechanical adhesion or chemical cross-linking. However, the Spiro composition is composed of natural polymeric materials, such as collagen and polysaccharide as indicated by the Title, Abstract, claims, and specification (e.g., column 1, lines 35 to 44). Similar to the Mizuno composition, the Spiro composition are in porous sponge-like forms. (column 1, line 66 to column 2, line 2; and column 2, lines 38 to 49)

Cook et al. is directed to hydrophobic biodegradable polymeric materials having one surface attached to a layer of hydrophilic polymer. (Abstract; and column 5, lines 29 to 49)

Sah et al. disclose methods of preparing a cultured, stratified cartilage tissue having two or more cartilage layers. The Sah composition is composed of natural polymers, such as collage, aggrecan, and hyaluronan. (paragraphs [0057], [0068], and Examples)

Contrary to the disclosures of Spiro et al., Cook et al., and Sah et al., the hydrogel of the present invention consist essentially of a hydrophilic and synthetic polymer network with high water content.

It is also important to note that none of Spiro et al., Cook et al., and Sah et al. suggests or even contemplates replacing the disclosed tissue construct of natural or hydrophobic polymers with synthetic and hydrophilic hydrogels as claimed by the present invention. Although Cook et al. use a hydrophilic polymer to modify the surface of a hydrophobic matrix, Cook et al. actually caution against overly using a hydrophilic material with the hydrophobic matrix because hydrophilic materials are considered less biodegradable than hydrophobic materials. Sah et al. particularly emphasize that the disclosed tissue construct closely replicates the natural cartilage tissue in structure and composition (paragraphs [0003], [0030], [0036], and [0037]). In view of such specific teachings of Sah et al., one skilled in the art would not be motivated to replace the natural polymers found in cartilage tissue with a synthetic hydrogel.

Anseth et al. are directed to a method of preparing a mono-layer hydrogel *in situ* via photopolymerization. Anseth et al. also describe medical benefits of fabricating polymers *in situ*. However, Anseth et al. do not suggest or contemplate a multi-layered hydrogel structure fabricated by partial gelling of each layers followed by further gelling for integration as claimed by the present invention. Nor Anseth et al. provide any suggestion or guidance for one skilled in the art to replace the natural polymers in the multi-layered constructs of Mizuno et al., Spiro et al., Cook et al., or Sah et al. with the referenced hydrogel.

Thus, the cited references in combination fail to advance any "apparent reason" for one of ordinary skill in the art to combine and modify the disclosed methods in such a particular manner to obtain the claimed invention.

Therefore, the claimed invention is not obvious over the combined disclosures of the cited references.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. 1.136(a)(3).

Should the Examiner have any remaining questions, she is invited to telephone the undersigned.

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